Manchester University
NHS Foundation Trust

DOCUMENT CONTROL PAGE

Title:	Chemotherapy Induced Nausea and Vomiting (CINV) Management Guidelines (Children's)
Version:	**4.2**
Supersedes:	4.1
Application:	Patients – Paediatric Haematology/Oncology patients receiving treatment with anticancer/chemotherapy agents All Staff

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Ratified by:	Paediatric Medicines Management Committee
Date of Ratification:	2nd August 2023

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Circulated by:	Authors
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Responsibility of:	Authors

Minor Amendment (If applicable) Notified To:	4.2 - Addition of nabilone to the treatment algorithm for the management of CINV
Date notified:	2nd August 2023

EqIA Registration Number:	128/13R

1 Introduction

Chemotherapy induced nausea and vomiting (CINV) is one of the most documented distressing side effects of childhood cancer and is a major limiting factor to compliance and effective treatment if not managed appropriately. Left untreated, it can lead to electrolyte imbalance, poor nutrition, dehydration, prolonged hospitalisation, and reduced quality of life. CINV can be acute (0-24hours after first chemotherapy dose), delayed (24hours – 5 days post chemotherapy) and anticipatory (prior to the start of chemotherapy). Adequate control of CINV is crucial and owing to the physiological differences between acute and delayed CINV different therapeutic approaches may be required. Symptoms of nausea and vomiting may also arise as a result of other 'non-chemotherapy' related management of malignant disease (opioids, establishment of feeding regimes…etc). It is important that treatment is directed towards the underlying cause in order to manage symptoms effectively. The Children's Cancer and Leukaemia Group (CCLG) have produced a national framework document to guide local implementation, which has been used to guide the content of this Trust guideline.

2 Purpose/Scope

The following guidelines are for the management of chemotherapy induced nausea and vomiting in paediatric haematology/oncology and haemopoeitc stem cell transplant (HSCT) patients. The guidance should be used in conjunction with the individual patient's anti-emetic history. The scope of the guideline is to advise on the management of nausea and/or vomiting as a direct side effect of chemotherapy. These guidelines are for management of patients in the acute setting and are not intended for use in palliative/end of life care.

3.1 Roles and Responsibilities

- The Medicines Management Committee and the Chemotherapy Group will approve the content of the guideline
- The Pharmacy Medicines Management Team will make available the "Chemotherapy induced nausea and vomiting (CINV) management guidelines (Children's)" on the Trust's intranet
- The Chemotherapy Group will ensure the guideline is updated if legislation, recommendations, evidence or good practice change.
- Departmental managers will disseminate procedural documents and facilitate any further training or discussion required.
- All trust staff: It is the personal responsibility of all staff to follow Trust procedural documents.
- It will be the responsibility of the individual POSCUs to ensure that this guidance is ratified locally

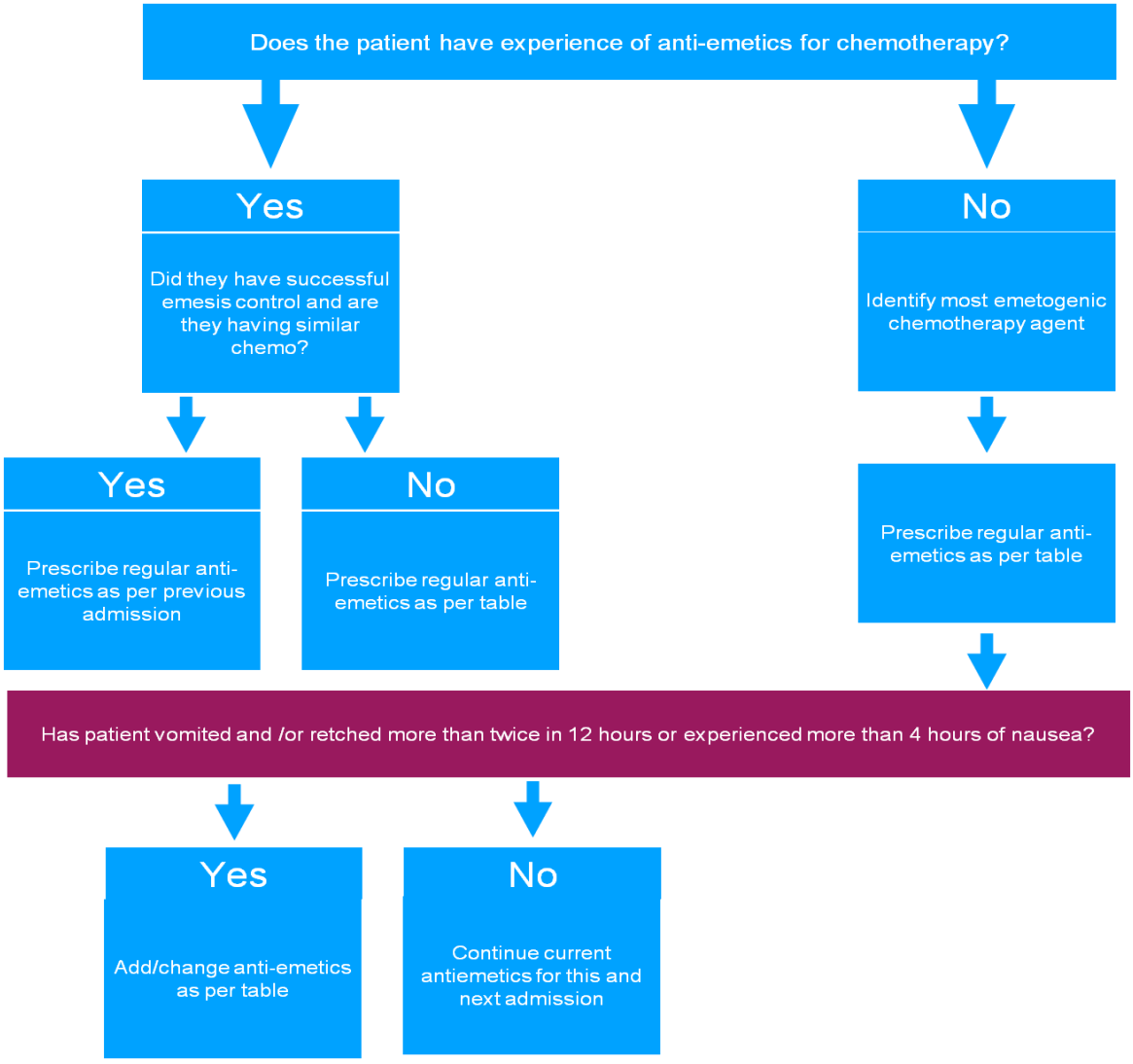
4 Recommendations : Over-riding principles

Patients being treated for malignant disease or undergoing HSCT can experience symptoms of nausea and vomiting for a number of different reasons including treatment with chemotherapy, establishing feeding and use of opioids. Symptoms can be distressing to both the patient and the family and can lead to refusal of further treatment if not managed effectively.

Children and young people about to undertake chemotherapy should have their chemotherapy assessed for emetogenicity. The CCLG have recommended chemotherapy be divided in to four strata:

- Very highly emetogenic chemotherapy (vHEC)
- Highly emetogenic chemotherapy (HEC)
- Moderately emetogenic chemotherapy (MEC)
- Minimally/Low emetogenic chemotherapy (min/LEC)

5. Flowchart: Overall step-wise approach to selecting anti-emetics



Prophylaxis: Very highly/highly emetogenic chemotherapy	
Individual drugs: Cisplatin Cyclophosphamide > 2g/m^2 Ifosfamide Melphalan Thiotepa *Combination chemotherapies:* Cyclophosphamide + anthracycline Cyclophosphamide + etoposide Etoposide + Ifosfamide Doxorubicin + Ifosfamide Cytarabine 300 mg/m^2 + etoposide Doxorubicin + methotrexate 5g/m^2	<u>Step 1:</u> • Ondansetron IV/PO + dexamethasone IV/PO + aprepitant PO (unless contraindicated) • Levomepromazine IV/PO + ondansetron IV/PO + dexamethasone IV/PO where there is a contraindication to aprepitant. • Levomepromazine IV/PO + ondansetron IV/PO + aprepitant PO where there is a contraindication to dexamethasone <u>Step 2:</u> • Add levomepromazine IV/PO where not used in step 1 • Contraindication to *both* aprepitant and dexamethasone OR uncontrolled CINV – levomepromazine continuous IV infusion or see Step 3. • Continuous IV infusion of dexamethasone with lorazepam may be considered. CONSULTANT DECISION ONLY or see Step 3. <u>Step 3:</u> • Add Nabilone PO short course CONSULTANT DECISION ONLY and after discussion in MDT. Not to be used with Levomepromazine and Lorazepam.

Prophylaxis: Highly emetogenic chemotherapy	
Actinomycin Carboplatin Carmustine Cyclophosphamide 1g/m^2 - 2g/m^2 Cytarabine 3g/m^2/dose Dacarbazine Methotrexate ≥8 g/m^2	<u>Step 1:</u> • Ondansetron IV/PO + dexamethasone IV/PO (unless contraindicated). • Ondansetron IV/PO + aprepitant PO where there is a contraindication to dexamethasone • Ondansetron IV/PO + levomepromazine IV/PO where there is a contraindication to both dexamethasone *and* aprepitant <u>Step 2:</u> • Add levomepromazine where not used in step 1 • Contraindication to *both* aprepitant and dexamethasone OR uncontrolled CINV – levomepromazine continuous IV infusion • Consider the addition of aprepitant PO *in subsequent cycles*, where CINV not controlled

<table>
<tr><th colspan="4">Prophylaxis: moderately emetogenic chemotherapy</th></tr>
<tr><td>Aldesleukin
Arsenic trioxide
Azacitidine
Cladribine
Clofarabine
Cyclophosphamide (< 1000mg/m^2)
Cytarabine (>200mg/m^2 to <3000mg/m^2)</td><td>Daunorubicin
Daunorubicin liposomal
Docetaxel
Doxorubicin
Etoposide
Idarubicin
Imatinib
Inotuzumab</td><td>Irinotecan
Lomustine
MTX (≥1000mg/m^2 to <12000mg/m^2)
Mitoxantrone
Procarbazine
Temozolomide
Treosulfan**</td><td><u>Step 1:</u>
• Ondansetron IV/PO + dexamethasone IV/PO (unless contraindicated).
• Ondansetron IV/PO + levomepromazine IV/PO where there is a contraindication to dexamethasone.

<u>Step 2:</u>
• Add levomepromazine IV/PO where not used in step 1
• Uncontrolled CINV – levomepromazine CIVI.
• Consider the addition of aprepitant in subsequent cycles, where CINV not controlled</td></tr>
<tr><th colspan="4">Prophylaxis: low/minimal emetogenic chemotherapy</th></tr>
<tr><td>Alemtuzumab
ATG
Asparginase
Bevacizumab
Bleomycin
Busulfan**
Chlorambucil</td><td>Dinutuximab
Blinatumumab
Cyclophosphamide (<300 mg/m^2)
Cytarabine (<200mg/m^2)
Fludarabine**
Gemcitabine
Gemtuzumab
Mercaptopurine
Methotrexate < 1g/m^2</td><td>Nelarabine
Rituximab
Tioguanine
Topotecan
Vinblastine
Vincristine
Vindesine
Vinorelbine</td><td><u>Step 1:</u>
• Often no prophylaxis required
• Single agent ondansetron IV/PO is required

Note: occasionally patients on low emetogenic chemotherapy require the addition of a second agent. At RMCH this agent of choice is levomepromazine or metoclopramide.</td></tr>
</table>

6. Management of breakthrough CINV

'Breakthrough' CINV refers to the reoccurrence of significant nausea and vomiting following a period of acceptable control. Where breakthrough CINV occurs management should be escalated to the next highest intensity level outlined in the tables above.

minEC → LEC → MEC → HEC→ vHEC

This should be clearly documented in the patient's notes and prophylaxis at the increased level should be considered for subsequent cycles of chemotherapy *where the same drug/combinations or drug/combinations of similar emetogenic potential are given.*

7. Refractory nausea or vomiting

'Refractory' CINV refers to the continuation of significant nausea or vomiting without a period of acceptable control.

Refractory CINV requires timely escalation of treatment to the next level up.

For patients with refractory nausea and vomiting on highly emetogenic chemotherapy regimens consider:

- Addition of aprepitant in subsequent cycles – review of previous contraindication
- Addition of levomepromazine continuous IV infusion
- Addition of dexamethasone with lorazepam continuous IV infusion – CONSULTANT DECISION ONLY
- Additional of lorazepam (PO or IV infusion)
- If the use of 3^{+} anti-emetics from different classes do not achieve adequate control, consider Nabilone CONSULTANT DECISION ONLY and after discussion in MDT.

8. Drug dosing and recommendations for use: *(alphabetical)*

<table>
<tr><th>Drug name</th><th>Dosing and administration</th><th>Side effects</th><th>Additional information</th></tr>
<tr>
<td>Aprepitant
Drug class:
NK1 receptor antagonist

Formulations:

125mg, 80mg capsule,

125mg powder for oral suspension</td>
<td>Administered orally 1 hour prior to chemotherapy on Days 1, 2 and 3.
<table>
<tr><th>Weight</th><th>Day 1</th><th>Day 2</th><th>Day 3</th></tr>
<tr><td><6kg</td><td colspan="3">Not recommended for <6 months old</td></tr>
<tr><td>6kg–7.9kg</td><td>25mg</td><td>15mg</td><td>15mg</td></tr>
<tr><td>8kg–9.9kg</td><td>30mg</td><td>20mg</td><td>20mg</td></tr>
<tr><td>10kg–11.9kg</td><td>35mg</td><td>25mg</td><td>25mg</td></tr>
<tr><td>12kg–14.9kg</td><td>45mg</td><td>30mg</td><td>30mg</td></tr>
<tr><td>15kg–19.9kg</td><td>60mg</td><td>40mg</td><td>40mg</td></tr>
<tr><td>20kg–24.9kg</td><td>75mg</td><td>50mg</td><td>50mg</td></tr>
<tr><td>25kg–29.9kg</td><td>90mg</td><td>60mg</td><td>60mg</td></tr>
<tr><td>30 kg and above</td><td>125mg</td><td>80mg</td><td>80mg</td></tr>
</table>
</td>
<td>Diarrhoea

Hiccups

Headache,

Decreased appetite

Cough

Neutropenia (slightly prolonged compared to without aprepitant).</td>
<td>Can increase Ifosfamide mediated neurotoxicity and Irinotecan toxicity. Monitor closely.

Caution where concomitant substances metabolised primarily through CYP3A4 and with a narrow therapeutic range – discuss with Pharmacy

Also p450 2c9 inducer. <u>Caution if given with the following:</u>
Etoposide, Ifosfamide Irinotecan, vincristine, vinblastine, vinorelbine,

<u>Avoid:</u> Phenytoin, carbamazepine, phenobarbitone, warfarin, benzodiazepines (lorazepam), clarithromycin and Rifampicin.

<u>Dexamethasone</u> give 50% dose
4mg/m^2 pre-chemotherapy
4mg/m^2/day during chemotherapy
8mg/m^2/day for 2 days post chemotherapy</td>
</tr>
</table>

<table>
<tr>
<td>Cyclizine
Drug class:
Antihistamine

Formulations:
50mg tablets, IV injection</td>
<td>IV/Oral:

<table>
<tr><th>Age</th><th>IV/Oral Dose</th></tr>
<tr><td>1 month–5 yrs</td><td>0.5-1mg/kg up to 3 times daily (Max 25mg/dose)</td></tr>
<tr><td>6–11 years</td><td>25mg up to 3 times daily</td></tr>
<tr><td>12 years+</td><td>50 mg up to 3 times daily</td></tr>
</table>
</td>
<td>Drowsiness

Dry mouth

Blurred vision

Urinary retention

Restlessness

Insomnia

Tachycardia</td>
<td>Avoid using with hyoscine and levomepromazine

Concomitant use with metoclopramide should be avoided where possible. Discuss with Pharmacy</td>
</tr>
</table>

<table>
<tr>
<td>Dexamethasone
Drug class:
Corticosteroid

Formulations:
2mg tablets
0.5mg tablets
2mg/5mL liquid
IV injection</td>
<td>Give 1st dose 30-60 mins before chemotherapy.

IV/Oral: <u>with</u> aprepitant
*do not increase dose until 24hr post last aprepitant dose
<table>
<tr><th></th><th>IV/Oral Dose</th></tr>
<tr><td>Loading dose</td><td>4mg/m^2 (max dose 8mg)</td></tr>
<tr><td>During chemotherapy</td><td>4mg/m^2/day in 3 divided doses</td></tr>
<tr><td>Post chemotherapy</td><td>8mg/m^2/day in 3 divided doses for TWO days</td></tr>
</table>
IV/Oral: <u>without</u> aprepitant
<table>
<tr><th></th><th>IV/Oral Dose</th></tr>
<tr><td>Loading dose</td><td>8mg/m^2 (max dose 12mg)</td></tr>
<tr><td>During chemotherapy</td><td>8mg/m^2/day in 3 divided doses</td></tr>
<tr><td>Post chemotherapy</td><td>8mg/m^2/day in 3 divided doses for TWO days</td></tr>
</table>
See appendix 1 for dexamethasone and lorazepam infusion</td>
<td>Adrenal suppression

Gastric irritation

Osteoporosis

Weight gain

Insomnia

Mood and behavioural problems</td>
<td>For maximum of 7 days

Dose of dexamethasone must be halved when used in combination with Aprepitant – see dosing information

<u>Contra-indicated (as anti-emetic)</u>:
Brain tumour patients, those already on steroids (allogenic BMT, SCT, and AML & ALL – discuss with consultant), patients on mifamurtide.</td>
</tr>
</table>

<table>
<tr>
<td>Levomepromazine
Drug class:
Phenothiazine

Formulations:
6mg tablet, 25mg Tablets
(tablets may be halved and dispersed)
IV Injection</td>
<td>
<table>
<tr><th>Age</th><th>IV/Oral Dose</th></tr>
<tr><td>1 month – 11 years</td><td>IV 0.05mg/kg twice a day
(max 12.5mg/dose)

PO 0.1mg/kg (max 3mg) twice a day</td></tr>
<tr><td>12-17 years</td><td>IV 0.05mg/kg BD (max 25mg/dose)

PO 3- 6.25 mg twice a day.
(max 25 mg twice daily)</td></tr>
</table>

Note: Doses may be increased as tolerated if ineffective. Max dose 1mg/kg twice daily (max 25mg twice daily).

<table>
<tr><th>Age</th><th>Continuous IV infusion</th></tr>
<tr><td>1month – 11 years</td><td>100-400 micrograms/kg over 24 hours
(max 25mg/24 hours)</td></tr>
<tr><td>12–17years</td><td>5-25mg over 24 hours
(max 25mg/24 hours)</td></tr>
</table>
</td>
<td>Somnolence

Asthenia

Dry mouth

Hypotension

Sedation

Site reaction

constipation</td>
<td>Monitor for drowsiness.

Avoid using with cyclizine and hyoscine, Use with caution with metoclopramide

Avoid use in hepatic impairment.
Reduce dose in renal impairment.

Can be useful in vomiting due to raised intracranial pressure.

Care in patients receiving ifosfamide since sedation may mask signs of encephalopathy.

IV – administer as slow IV infusion over 30 mins.</td>
</tr>
<tr>
<td>Lorazepam
Drug class:
Benzodiazepine

Formulations:
1mg &2mg tablets
(tablets may be halved),
IV Injection</td>
<td>Oral:

<table>
<tr><th>Age</th><th>Recommendation</th></tr>
<tr><td>< 5 years</td><td>Not recommended</td></tr>
<tr><td>5–10 years</td><td>0.5mg up to 3 times daily</td></tr>
<tr><td>10 years+</td><td>1mg up to 3 times daily</td></tr>
</table>

See appendix 1 for dexamethasone and lorazepam infusion</td>
<td>Drowsiness

Amnesia

Confusion and ataxia</td>
<td>Use of oral preparation for anticipatory nausea and vomiting only.

For use as a continuous IV infusion with dexamethasone see algorithm in appendix 1. This should only be done under the direction of a Consultant after all other treatment has failed.</td>
</tr>
</table>

<table>
<tr>
<td>Metoclopramide
Drug class:
Dopamine antagonist

Formulations:
10mg Tablets
5mg/5mL liquid
10mg/2ml Injection</td>
<td>
IV/Oral: See MHRA alert 2013.

<table>
<tr><th>Age</th><th>Recommendation</th></tr>
<tr><td>< 1 year</td><td>Not recommended</td></tr>
<tr><td>1–18 years</td><td>0.15mg/kg three times a day
(Maximum 10mg per dose TDS)</td></tr>
</table>

OR
<table>
<tr><th>Weight</th><th>Oral/IV Dose</th></tr>
<tr><td>10–14.9kg</td><td>1mg three times a day</td></tr>
<tr><td>15–19.9kg</td><td>2mg three times a day</td></tr>
<tr><td>20–29.9kg</td><td>2.5mg three times a day</td></tr>
<tr><td>30–60kg</td><td>5mg three times a day</td></tr>
<tr><td>>60kg</td><td>10mg three times a day</td></tr>
</table>
</td>
<td>Extrapyramidal effects

Hyper-prolactinaemia

Drowsiness

Restlessness</td>
<td>Review with consultant before using. Duration should not exceed 5 days.

Use after levomepromazine failed. Do not use with levomepromazine.

Reduce dose in renal and hepatic impairment

Use with caution with cyclizine and hyoscine – will reduce prokinetic effects

Treat dystonic reactions with IV bolus of PROCYCLIDINE:
<table>
<tr><td><2 yrs.</td><td>0.5-2mg as a single dose</td></tr>
<tr><td>2–10 yrs.</td><td>2-5mg as a single dose</td></tr>
<tr><td>>10 yrs.</td><td>5-10mg as a single dose</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Nabilone
Drug class:
Cannabinoids
<u>Schedule 2 (CD)</u>

Formulations:
250 micrograms capsules
1mg capsules</td>
<td>Oral:

<table>
<tr><th>Age</th><th>Recommendation</th></tr>
<tr><td>< 4 years</td><td>Not recommended</td></tr>
<tr><td>≥ 4 years</td><td>See dosing below</td></tr>
</table>

<table>
<tr><th>Weight</th><th>Oral Dose</th></tr>
<tr><td><18kg</td><td>0.5mg 12 hourly</td></tr>
<tr><td>18-30kg</td><td>1mg 12 hourly</td></tr>
<tr><td>>30kg</td><td>1mg 8-12 hourly</td></tr>
</table>
</td>
<td>Drowsiness

Abdominal pain

Hallucination
Vertigo/visual impairment

Euphoria

Gastro-intestinal side effects (e.g., abdominal pain, reduced appetite)</td>
<td>Consultant decision to commence after MDT discussion.

Avoid in severe hepatic impairment.

Only prescribed with vHEC where at least 3 anti-emetics from different classes have been used with no benefit.

Treatment starts night before chemotherapy due, second dose to be administered 1-3 hours before chemotherapy and can be continued for 24-48 hours post chemotherapy dose.

Cautions: Heart disease, psychiatric disorders, hypertension. Monitor behavioural effects/mood, adverse effects on mental state can persist 48-72 hrs after stopping.

Not to be used with levomepromazine and lorazepam.</td>
</tr>
</table>

<table>
<tr>
<td>Ondansetron
Drug class:
5HT₃ antagonist

Formulations:
4mg tablets
8mg tablets
4mg/5mL liquid
2mg/ml IV injection</td>
<td>IV/Oral: CINV
<table>
<tr><th>Age</th><th>Oral/IV Dose</th></tr>
<tr><td>< 1 month</td><td>0.15mg/kg three times a day</td></tr>
<tr><td>1 month –18 years</td><td>5mg/m² three times a day
(max 8mg/dose)</td></tr>
</table>
OR for oral dosing (outpatient/discharge)
<table>
<tr><th>Weight</th><th>SA m²</th><th>Oral Dose</th></tr>
<tr><td>4–6.5kg</td><td>0.26–0.36</td><td>1.6mg three times a day</td></tr>
<tr><td>6.6–10kg</td><td>0.37–0.49</td><td>2mg three times a day</td></tr>
<tr><td>10.1–16kg</td><td>0.5–0.68</td><td>3mg three times a day</td></tr>
<tr><td>16.1–29.9kg</td><td>0.69–1</td><td>4mg three times a day</td></tr>
<tr><td>30–38.9kg</td><td>1.01–1.2</td><td>6mg three times a day</td></tr>
<tr><td>>39 kg</td><td>>1.2</td><td>8mg three times a day</td></tr>
</table>
</td>
<td>Constipation

Headache

Flushing

Occasional diarrhoea</td>
<td>Reduce dose in moderate or severe hepatic impairment

Do not use with drugs that prolong QT interval

Dosing for CINV only.</td>
</tr>
</table>

9. Equality, Diversity and Human Rights Impact Assessment.

This document has undergone and Equality, Diversity and Human Rights Impact Assessment. It has been assigned a unique EqIA registration number, please see document control page.

10. Consultation, Approval and Ratification Process

10.1 Consultation Process, Consultation and Communication with Stakeholders
Paediatric Haematology/Oncology Team

10.2 **Policy Approval Process**
Paediatric Chemotherapy Group

10.3 **Ratification Process**
Paediatric Medicines Management Committee

11. Dissemination and Implementation

11.1 Dissemination

The document will be circulated to the Consultants, Lead Nurse for Haematology/Oncology (Children's Division) and Pharmacy via the Chemotherapy Group.

This guideline will be available on the Trust intranet site

Dissemination to the POSCU centres will be through the MacMillan Team and the Paediatric Cancer Administration and Quality Manager

12. Monitoring Compliance of Procedural Documents

Process for Monitoring Compliance.

Compliance with the guideline will be monitored during daily clinical ward visits. No formal audit of compliance is required.

13. References and Bibliograph

1. Paediatric Formulary Committee. BNF for children [online] Available from www.medicinescomplete.com [accessed: 22/06/18].
2. Children's Cancer and Leukaemia Group (CCLG), "Guideline on the management of chemotherapy induced nausea and vomiting" CCLG Supportive Care Group, Version 1, 2018
3. Tomlin S., 2018. Guy's and St Thomas' Paediatric Formulary [online] Available from http://cms.ubqo.com/public/d2595446-ce3c-47ff-9dcc-63167d9f4b80 [accessed22/06/18].

4. Dupuis LL, Nathan PC. Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Paediatr Drugs. 2003;5(9):597-613. doi: 10.2165/00148581-200305090-00003 [Accessed 12/05/23]
5. Simonian JS, Varanasi S, Richards GJ, Nguyen AV, Diaz-Fong JP, Le J. A critical narrative review of medical cannabis in pediatrics beyond epilepsy, part III: chemotherapy-induced nausea and vomiting and inflammatory bowel disease. Pediatr Med 2020;3:12. doi: 10.21037/pm-20-70 [Accessed 12/05/23]

Appendix 1: Dexamethasone and Lorazepam Infusion pump guideline

(Consultant direction only)

Patients receiving chemotherapy regimens with a very high emetogenic potential may require the use of a continuous infusion of dexamethasone and to control symptoms of nausea and vomiting.
Refer to the table on page 3 for examples of very highly emetogenic chemotherapy.
All patients must be discussed with the Consultant prior to commencing a dexamethasone/ lorazepam infusion.

If the decision to commence an infusion is made please prescribe as follows:

(note: doses may differ from those listed in the BNF-C/SPC. Doses used are based on national experience and are established practice)

Drug	**Dose**	**Infusion Fluid**	**Rate**	**Review**
Dexamethasone	8mg/m^2/day	Combine in syringe and make up to a total volume of 48mls with Glucose 5%	2ml/hr over 24 hours. Commence at least 1 hour before chemotherapy is started	Daily and before each subsequent cycle of chemotherapy
Lorazepam	0.05mg/kg/day (50micrograms/kg/day)			